REMARKS/ARGUMENTS

In this Amendment, claims 1 and 93 are currently amended; claims 2-37, 60-75, 77-92 and 94-96 were previously presented; and claims 38-59 and 76 are cancelled without prejudice or disclaimer. New claims 97-113 have been added to more completely describe Applicants' invention. The amended and new claims are fully supported by the instant specification and the prior and pending claims. Accordingly, no new matter is introduced by the amended and new claims.

The presently pending claims in this application are claims 1-37, 60-75 and 77-113.

Applicants respectfully point out that the Docket No. for this application has been changed to **28069-594**.

The claims fulfill the requirements of 35 U.S.C. § 112, first paragraph

Claims 1-37, 60-75, 77-89, 91 and 92 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled for a release controlling shell of biocompatible and biodegradable polymers other than PLGA. In this regard, the Examiner opines that the "claims are so broad that they read on any polymer known to man."

Applicants respectfully disagree with this rejection. Applicants' claims recite that the release controlling shell that comprises a biocompatible and biodegradable polymer. Therefore, one having skill in the pertinent art would know that not "any polymer known to man" would be suitable for use. Rather, based on the claim elements considered as a whole, those skilled in the art would look to polymers that have the biological parameters specified by Applicants and that form a film or shell around a microparticle so as to distinguish the claimed polymers from just any polymer.

It is further noted that at the time of the present invention, one having skill in the art would have been aware of various types of biocompatible and biodegradable polymers, in addition to PLGA, that would be suitable for use in the present invention. In particular, the instant specification makes reference to art that discloses suitable types of biocompatible and

biodegradable polymers. See, for example, the instant specification on page 37, lines 19-24, which references international publication WO 97/14408. This citation, in turn, discloses, for example, on page 8, lines 7-27, various polymers that are suitable for shells or films in accordance with Applicants' presently claimed invention.

In view of the knowledge of the skilled practitioner in the relevant art at the time of the present invention, it is submitted that no undue experimentation would be required to practice the full scope of the presently claimed invention. It is further submitted that the full scope of Applicants' presently claimed invention could be practiced with a reasonable expectation of success in view of the teaching of the present application, combined with knowledge in the art at the time.

Additionally, the original claims in the instant application describe that the release controlling shell may be formed by a homopolymers or copolymer containing alpha-hydroxy acid units (original claim 36) and that the alpha-hydroxy acid may be lactic acid and/or glycolic acid (original claim 37). Given that the claims of an application form part of the disclosure, the original specification offers ample support for the broader recitation of "a release controlling shell of biocompatible and biodegradable polymers" suitable for use in accordance with the presently claimed invention. In view of Applicants' own teaching and the knowledge in the art at the time of the invention, the metes and bounds of the presently claimed invention would be fully understood and able to be practiced without undue experimentation by the skilled person in the pertinent art.

It is thus submitted that the instant specification, combined with knowledge of those having skill in the pertinent art, provide support for more than PLGA as a release controlling polymer in the claimed invention. Accordingly, withdrawal of the § 112, first paragraph rejection is respectfully requested.

The claims fulfill the requirements of 35 U.S.C. § 103(a)

Claims 1-37, 60-75 and 77-96 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Woiszwillo et al. (U.S. Patent No. 5,981,719, of record), hereinafter "Woiszwillo", and Ekman et al. (U.S. Patent No. 4,822,535, of record), hereinafter "Ekman", in

view of Laakso et al. (*J. Pharm. Sci.*, 1986, 75(10):962-967, of record), hereinafter "Laakso", Takada et al. (U.S. Patent No. 5,622,657, of record), hereinafter "Takada", and WO 97/14408.

The rejection of the claims under 35 USC § 103(a) is respectfully traversed. Applicants respectfully contend that the Examiner has not established a *prima facie* case of obviousness under 35 U.S.C. § 103 as a basis for rejection of the recited claims.

The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time of the invention "to prepare the claimed microparticles by employing the method of Woiszwillo followed by that of Ekman." The Examiner has further alleged that there is motivation because "Woiszwillo's method is to prepare a microparticle and then Ekman would further encapsulate such microparticle to increasing [*sic*] the stability of the biological [*sic*] active substances." (12/28/2004 and 10/07/2005 Office Actions, page 8).

It is pointed out that the instant disclosure addresses the clear distinctions between the presently claimed invention and the teaching of Woiszwillo. Indeed, as described by Applicants, Woiszwillo teaches manufacturing processes and conditions that are not suitable for sensitive proteins as biologically active substances. Woiszwillo's process involves exposure to chemical modification or harmful temperatures. Woiszwillo's process also produces microspheres having a size distribution that is too narrow for parenteral, sustained release and which complicates the post-manufacture processing of the microspheres. In contrast, Applicants' claimed invention preserves activity and/or function of the biologically active substance comprising the microparticles and forms microparticles having a size suitable for sustained released following parenteral administration.

Specifically, on page 9, lines 20-35 to page 10, lines 1-26 of the instant disclosure, Applicants teach the following with regard to Woiszwillo:

> Alternative methods for the manufacture of microspheres in two-phase aqueous systems have been described. In US 5 981 719 [Woiszwillo], microparticles are made by mixing the biologically active macromolecule with a polymer at a pH close to the isoelectric point of the macromolecule and stabilizing the microspheres through the supply of energy, preferably heat. The lowest percentage of macromolecule, i.e. the biologically active substance, in the preparation is 40%, which for most applications is too high and leads to great

> uncertainty in the injected quantity of active substance, since the dose of microparticles becomes far too low. Even though the manufacturing method is described as mild and capable of retaining the biological activity of the entrapped biologically active substance, the microparticles are stabilized by heating and, in the examples given, heating is effected to at least 58°C for 30 min. and, in many cases, to 70-90°C for an equivalent period, which cannot be expected to be tolerated by sensitive proteins, the biological activity of which is dependent on a three-dimensional structure, and even where the protein has apparently withstood the manufacturing process, there is still a risk of small, but nonetheless not insignificant changes in the conformation of the protein. As the outer phase, a combination of two polymers is always used, generally polyvinyl pyrrolidone and PEG, which complicates the manufacturing process in that both these substances have to be washed off from the microspheres in a reproducible and safe way. The microparticles formed are too small (in the examples, values below 0.1 μm in diameter are quoted) to be suitable for parenteral sustained release after, for example, subcutaneous injection, since macrophages, which are cells specialized in phagocytizing particles and which are present in the tissues, are easily capable of phagocytizing microspheres up to 5-10, possibly 20 μm, and the phagocytized particles are localized intracellularly in the lysosomes, where both the particles and the biologically active substance are degraded, whereupon the therapeutic effect is lost. The very small particle size also makes the processing of the microspheres more complicated, since desirable methods, such as filtration, cannot be used.

Thus, Woiszwillo's teaching is inapposite to the presently claimed invention, which does not involve elevated temperatures and which produces particles of a different size, i.e., a mean particle diameter size within the range of 10-200 μm, in the dry state. Unlike Woiszwillo, Applicants' process involves the use of a concentrated biologically active agent admixed with a starch solution to form an emulsion of starch droplets containing biologically active substances. These droplets are subsequently solidified and dried to form microparticles that are then coated on their outer surface with a release controlling shell.

Ekman's teaching in no way relates to "further encapsulating a microparticle". Ekman's method involves trapping or enclosing a macromolecular substance within a microparticle while the microparticle is being formed in an aqueous medium. (See, Col. 8, lines 8-17 of Ekman). Combining this teaching with that of Woiszwillo does not arrive at Applicants' claimed method. Further, Ekman does not remotely teach or disclose a method of making microparticles that involves coating pre-formed, solid particles with an outer shell of a release rate-controlling polymer, where an organic solvent would be used.

Applicants have previously explained that there is no suggestion provided by the art to combine the method of Woiszwillo with the method of Ekman. There is simply no motivation provided by the references that would lead one having skill in the art to make the modifications that would be necessary to achieve Applicants' claimed invention from the combination. Combining the teaching of Woiszwillo, which describes a distinct process, with the teaching of Ekman in no way leads one to arrive at Applicants' invention as presently claimed.

Since Woiszwillo's process involves a means to stabilize microspheres produced by Woiszwillo's process, there is no motivation for one to look to Ekman for a teaching relating to microparticle stabilization. For the sake of argument only, if Ekman's method were used following Woiszwillo's method of making microspheres, as is postulated by the Examiner, this still would not make Applicants' claimed invention obvious, because Ekman simply does not teach or suggest a method that requires applying a film or coating of a release controlling polymer to the surface of dried microparticles as is described by Applicants' claimed invention.

Without a suggestion or motivation in the references to combine their teachings, the § 103 rejection is inappropriate and should be withdrawn.

Moreover, it is submitted that, taken together, the supplemental references of Laakso, which teaches that polyacryl starch may be used as a carrier for passive target drug delivery; Takada, which teaches a sustained release formulation biologically active microparticles coated by copolymers of polylactic/glycolic acid; and WO 97/14408, which describes air suspension technology for producing sustained release microparticles, do not compensate for the severe deficiencies of the primary and secondary references in combination. These supplemental references teach discrete components in the art. Moreover, the art offers no suggestion or motivation to combine these components in a way that would render the presently claimed invention obvious.

The combination of Woiszwillo, Ekman, Laakso, Takada and WO 97/14408 does not teach Applicants' presently claimed method, in consideration of all of its steps and required elements, taken as a whole. Indeed, none of the references, alone or in combination, teach Applicants' process involving the concentration or solidification of a biologically active

substance into microparticles for parenteral sustained release, without exposure of the substance to organic solvents or high temperatures. The combination of cited art does not arrive at Applicant's method that produces microparticles allowing the biological substance to retain its activity and/or function and being of a size that avoids phagocytosis by tissue macrophages.

Applicants assert that all claim limitations must be taught or suggested by the cited art reference. M.P.E.P. §2143.03. However, the applied references, alone or in combination, do not teach or suggest all of the limitations of Applicants' presently claimed invention. Specifically, Woiszwillo, Ekman, Laakso, Takada and WO 97/14408, in combination, fail to teach a process in which a concentrated form of a biologically active substance is formed from an emulsion into starch microparticles, dried into solid form, and then coated with a biodegradable and biocompatible release-controlling polymer, e.g., PLGA, shell or film in the presence of an organic solvent, where neither the biologically active substance nor its activity/function is harmed by the process.

Based on the foregoing, as well as on Applicants' previous remarks of record, withdrawal of the 35 U.S.C. §103(a) rejection is respectfully requested.

CONCLUSION

Applicants respectfully submit that the application is now in condition for allowance. An action progressing this application to issue is courteously urged.

Should any additional fees be deemed to be properly assessable in this application for the timely consideration of this Amendment, or during the pendancy of this application, the Commissioner is hereby authorized to charge any such additional fee(s), or to credit any overpayment, to Deposit Account No. **50-0311**, Reference No. **28069-594**.

Should a further Extension of Time be required in connection with the filing of this Amendment, the Commissioner is hereby requested to grant any such Extension of Time as may be deemed necessary, and is authorized to charge any such Extension of Time Fee as may be required to keep the application in good standing, to Deposit Account No. **50-0311**, Reference No. **28069-594**.

If the Examiner believes that further discussion of the application would be helpful, he is respectfully requested to telephone the applicants' undersigned representative at (212) 692-6742 and is assured of full cooperation in an effort to advance the prosecution of the instant application and claims to allowance.

Respectfully submitted,

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